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No venous thromboembolic (VTE) recurrence after one-year follow-up of hospitalized COVID-19 patients diagnosed with VTE event: a prospective study

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Research letter

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ABBREVIATION LIST: COVID-19 = Coronavirus disease; CTPA = computed tomography pulmonary angiography; DVT = deep vein thrombosis; ICU = intensive care unit; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; SARS-CoV-2 = severe acute respiratory syndrome coronavirus; UFH = unfractionated heparin; VTE = venous thromboembolic event

KEYWORDS: COVID-19; recurrence; deep vein thrombosis; pulmonary embolism; anticoagulation

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To the Editor:

Since the beginning of the pandemics, a high prevalence of venous thromboembolic events (VTE) has been observed in hospitalized patients with severe coronavirus disease-2019 (COVID-19).[1] Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection induces major endothelial cell dysfunction with systemic inflammatory response, both resulting in micro- and macrovascular thrombotic events including pulmonary thrombosis/embolism.[1,2] While multiple studies evaluated the efficacy and safety of anticoagulant therapy in COVID-19 patients with diagnosed VTE during hospital stay, limited data are available regarding outcomes after hospital discharge.[3-7] Notwithstanding the particular pathogenesis of thrombosis in COVID-19 patients, whether SARS-CoV-2 infection is an effective transient VTE risk factor requiring 3-6 month anticoagulant therapy[8] is still debated. We aimed to investigate the outcome of COVID-19 patients with diagnosed VTE during hospital stay, while on anticoagulant therapy and after its discontinuation over one-year follow-up.

Methods

We conducted a prospective observational cohort study in our university hospital intensive care unit (ICU) and medical wards. We included all consecutive COVID-19 patients with VTE diagnosed during hospitalization from 03-25-2020 to 04-30-2021, further referred after hospital discharge to our outpatient thrombosis unit for follow-up. SARS-CoV-2 infection was diagnosed using standard RT-PCR (Cobas-SARS-CoV-2 kits®-Roche, France). COVID-19-related symptomatic VTE, namely pulmonary embolism (PE) and/or deep vein thrombosis (DVT), were diagnosed using computed tomography pulmonary angiography (CTPA) and/or duplex ultrasound examination of the lower limb veins by certified ultrasound operators, respectively. Laboratory thrombophilia screening was performed within 24h of DVT/PE diagnosis (**Table1**). VTE prophylaxis and management followed local guidelines in agreement with the international guidelines regarding ICU/non-ICU COVID-19 patients[8]. In DVT/PE patients, we recommended initial anticoagulant therapy with low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) if contraindicated, switched on discharge to direct oral anticoagulant (DOAC; creatinine clearance≥30mL/min). For most patients, in the absence of evidence, a 3-6-month

duration of anticoagulant treatment was proposed, as recommended elsewhere.[8] Outcome criteria included symptomatic VTE recurrence (primary outcome) and bleeding event onset (secondary outcome). Visits were planned at 1, 3, 6, and 12 months after VTE diagnosis, and beyond if needed. Periodic evaluation included physical examination to assess both outcomes and when required, duplex ultrasound examination, CTPA, and laboratory reassessment of abnormal thrombophilia parameters if needed away from the acute phase. Bleeding events were adjudicated according to the ISTH criteria.[9] This study was part of the French COVID-19 cohort registry, approved by our institutional ethics committee (IDRCB-2020-A00256-33; CPP-11-20-20.02.04.68737). All participating patients gave their written informed consent. Reporting of the study conforms to broad EQUATOR guidelines. Quantitative variables were expressed as medians [25^{th}-75^{th} percentiles] and categorical variables as percentages (MedCalc®-version11.0.1.0, Belgium).

Results

Over the 13-month study period, of the 59 discharged patients who developed COVID-19 related VTE during hospital stay, 48 patients (age, 62 years [52-67], 38M/10F) were followed in our outpatient thrombosis unit and included in the study (11 patients declined the follow-up). Median follow-up duration was 12 months [12-14], of which 6 months [5.5-6.6] after anticoagulant discontinuation. One patient was lost to follow-up after the first visit. Hospitalization baseline clinical and laboratory characteristics are reported in **Table1**. During hospitalization, 40 patients (83%) presented PE (of which 8 with associated DVT); 8 patients (17%) had isolated DVT. Antiphospholipid antibodies initially present in 26 patients (54%) persisted in only four patients (8%) after 12 weeks. Forty patients (83%) received LMWH, 2 (4%) UFH and 6 (13%) DOAC (3 apixaban and 3 rivaroxaban) for initial VTE management. After discharge, 45 patients (94%) received DOAC (35 apixaban, 10 rivaroxaban) and three (6%) received LMWH. Anticoagulants were discontinued after 3 months in one DVT patient (2%) and 6 months in 38 additional patients (79%). Anticoagulants were continued in eight patients (16%) in relation to antiphospholipid syndrome (n=3), past VTE history (n=2) and underlying cancer (n=3).

Outcomes during follow-up are summarized in **Figure1**. No symptomatic VTE recurrence was observed neither during nor after anticoagulant therapy discontinuation. One 66-year-old patient with a 6-year history of ischemic cardiomyopathy developed non-ST-elevation myocardial infarction five months after apixaban initiation and underwent coronary stenting with apixaban switch to dual antiplatelet therapy. During the anticoagulant therapy period, five patients (11%) presented bleedings including three major hemorrhages affecting the gastrointestinal tract (2 in-hospital, 1 post-discharge) and two minor episodes (both post-discharge). One major bleeding patient further developed confirmed heparin-induced thrombocytopenia, requiring heparin switch to argatroban, then danaparoïd, and finally to apixaban without bleeding recurrence. In addition, once anticoagulation was stopped, one 66-year-old man with past polycythemia vera (6-month apixaban for PE, then switched to aspirin), died 9 months later from major duodenal hemorrhage (**Figure1**).

Discussion

To the best of our knowledge, this is one of the first prospective real-life studies evaluating outcomes over 12-months following COVID-19-related VTE diagnosis in hospitalized patients. We report the absence of VTE recurrence during the follow-up on anticoagulant therapy and after discontinuation. Only few studies reported shorter follow-up (from 10 to 159 days) in cohorts of 24 to 737 COVID-19-related VTE patients,[3-7] showing a very low rate of VTE recurrence (0.0 to 2.4%) during anticoagulant therapy, consistently with our data. Moreover, we provided new data confirming the low VTE recurrence risk up to 6 months after anticoagulant discontinuation. This low risk in COVID-19 patients is similar to what is observed in patients with VTE provoked by a transient non-surgical factor.[10] Our data support limited anticoagulant therapy duration of 3-6 months in COVID-19 patients, in agreement with current guidelines,[8] although selected individuals (e.g., with a past VTE history) may require long-term anticoagulation. The rate of major bleedings (6.3%) on anticoagulant therapy in our cohort was comparable to those reported in previous studies (2.6 to 11.0%)[3-7] but heterogeneity of patient recruitment and anticoagulant management across studies makes comparisons difficult.

Despite limitations due to its single-center design and small sample size, our study presents significant strengths such as the inclusion of critically and non-critically ill COVID-19 patients. Moreover, by contrast to other studies, we report outcomes after a relatively long-term anticoagulant therapy discontinuation.

To conclude, our study with prospective one-year follow-up supports the low VTE recurrence risk in either critically or non-critically ill COVID-19 patients with VTE while on anticoagulant therapy and 6-month after its discontinuation. Our data remain to be confirmed in larger cohorts.

References

1- Jiménez D, García-Sanchez A, Rali P, et al. Incidence of VTE and Bleeding Among Hospitalized Patients With Coronavirus Disease 2019: A Systematic Review and Meta-analysis. *Chest.* 2021;159(3):1182-1196.

2- Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2020;75(23):2950-2973.

3- Doyle AJ, Thomas W, Retter A, et al. Updated hospital associated venous thromboembolism outcomes with 90-days follow-up after hospitalisation for severe COVID-19 in two UK critical care units. *Thromb Res*. 2020;196:454-456.

4- Demelo-Rodríguez P, Ordieres-Ortega L, Ji Z, et al. Long-term follow-up of patients with venous thromboembolism and COVID-19: Analysis of risk factors for death and major bleeding. *Eur J Haematol*. 2021;106(5):716-723.

5- Fernández-Capitán C, Barba R, Díaz-Pedroche MDC, et al. Presenting Characteristics, Treatment Patterns, and Outcomes among Patients with Venous Thromboembolism during Hospitalization for COVID-19. *Semin Thromb Hemost.* 2021;47(4):351-361.

6- Buso G, Mazzolai L, Rueda-Camino JA, et al. Pulmonary Embolism in Patients with COVID-19: Comparison between Different Care Settings. *Semin Thromb Hemost.* 2021 (in press).

7- Whyte MB, Barker R, Kelly PA, et al. Three-month follow-up of pulmonary embolism in patients with COVID-19. *Thromb Res.* 2021;201:113-115.

8- Moores LK, Tritschler T, Brosnahan S, et al. Prevention, Diagnosis, and Treatment of VTE in Patients With Coronavirus Disease 2019: CHEST Guideline and Expert Panel Report. *Chest.* 2020;158(3):1143-1163.

9- Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost.* 2005;3(4):692-694.

10- Iorio A, Kearon C, Filippucci E, et al. Risk of recurrence after a first episode of symptomatic venous thromboembolism provoked by a transient risk factor: a systematic review. *Arch Intern Med.* 2010;170(19):1710-1716.

11- Revel MP, Parkar AP, Prosch H, et al. European Society of Radiology (ESR) and the European Society of Thoracic Imaging (ESTI). COVID-19 patients and the radiology department - advice from the European Society of Radiology (ESR) and the European Society of Thoracic Imaging (ESTI). *Eur Radiol*. 2020;30(9):4903-4909.

Figure to legend

Figure 1 – Bleeding and thromboembolic events during 1-year follow-up in 48 COVID-19 patients presenting with a venous thromboembolic event diagnosed during hospitalization for COVID-19. The timeline indicates the date of clinical event occurrence after discharge (M=month). DVT, deep vein thrombosis; HIT, heparin induced thrombocytopenia; ICU, intensive care unit; LMWH, low molecular weight heparin; PE, pulmonary embolism; RBC, red blood cells; UFH, unfractionated heparin; VTE, venous thromboembolic event.

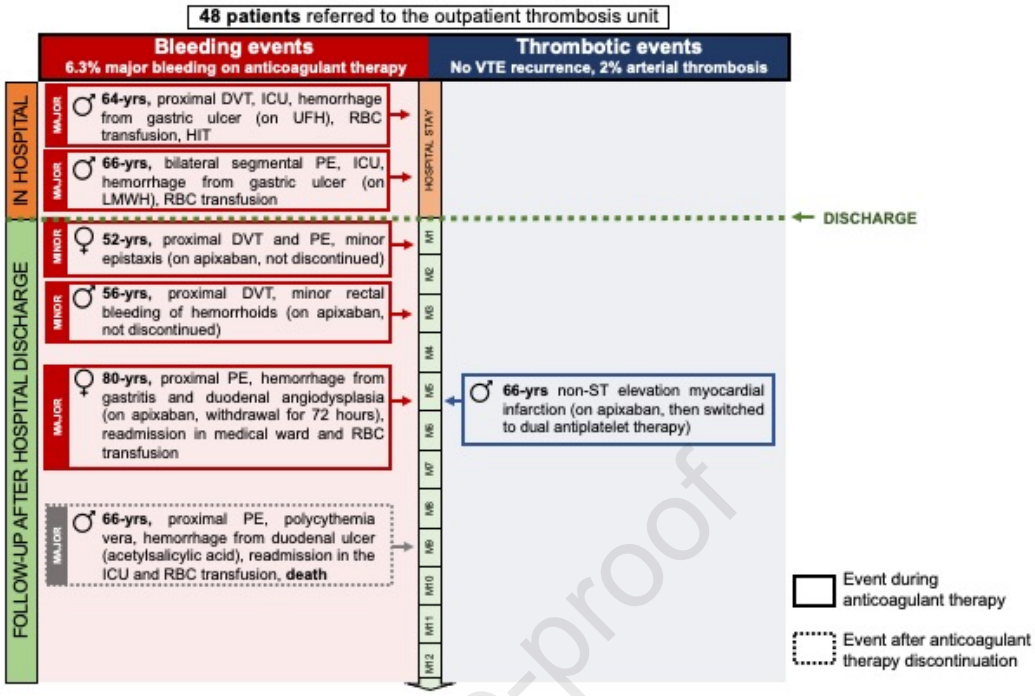
Table 1. Initial clinical and laboratory characteristics in 48 COVID-19 patients with diagnosed thromboembolic events

Patients characteristics	
Age (years)	62 [52-67]
Male gender, n (%)	38 (79)
Body mass index (kg/m^2)	27.0 [24.3-30.0]
Hypertension, n (%)	17 (35)
Diabetes, n (%)	13 (27)
History of cardiac disease, n (%)	8 (17)
Past VTE history, n (%)	6 (12)
COVID-19-related lung involvement[†]	
<10%, n (%)	4 (8)
10-25%, n (%)	15 (31)
25-50%, n (%)	15 (31)
50-75%, n (%)	14 (30)
Critically ill patients, n (%)	17 (35)
Time from first symptoms to VTE diagnosis (days)	12 [9-16]
Time from hospital admission to VTE diagnosis (days)	0 [0-4]
Description of VTE	
Pulmonary embolism, n (%)	40 (83)
Proximal, n (%)	36 (75)
Isolated, n (%)	32 (67)
Bilateral, n (%)	19 (40)
Deep vein thrombosis, n (%)	16 (33)
Proximal, n (%)	8 (17)
Isolated, n (%)	8 (17) (6 in the ICU)

Bilateral, n (%)	2 (4)
Initial anticoagulant therapy	
Low-molecular weight heparin (therapeutic dose), n (%)	40 (83)
Direct oral anticoagulant, n (%)	6 (13)
apixaban	3 (6)
rivaroxaban	3 (6)
Unfractionated heparin (therapeutic dose), n (%)	2 (4)
Anticoagulant therapy on hospital discharge	
Direct oral anticoagulant, n (%)	45 (94)
Apixaban	35 (73)
Rivaroxaban	10 (21)
Low molecular weight heparin (therapeutic dose), n (%)	3 (6)
Length of hospital stay (days)	11 [7-18]
Laboratory data	
Hemoglobin (g/dL)	12.7 [11.4-13.3]
Platelet count (G/L)	323 [255-386]
Leukocytes (G/L)	8.2 [6.8-10.3]
Serum creatinine (µM)	72.0 [59.0-84.0]
Fibrinogen (g/L)	5.89 [4.8-7.8]
D-dimer (ng/mL)	3,410 [1,990-8,450]
Antiphospholipid antibodies	
Lupus anticoagulant, n (%)*††	24 (50)
Anti-cardiolipin and/or anti-beta-2-GPI antibodies, n (%)**	7 (15)
Persistence of anti-phospholipid antibodies ≥12 weeks, n (%)	4 (8)
*Antithrombin activity****†† (IU/dL)*	92 [85-102]
*Protein C clotting activity****†† (IU/dL)*	82 [66-93]

*Protein S****††	
Clotting activity†† (IU/dL)	58 [41-75]
Free antigen†† (IU/dL)	88 [71-111]
F2 G20210A variant, n (%)	4 (8)
F5 G1691A variant, n (%)	2 (4)

Results are expressed as median [interquartile range]. VTE, venous thromboembolic event. Thrombophilia screening parameters are written in *italic*; †COVID-19-related lung involvement (%) refers to parenchymal ground-glass opacities based on CT findings as defined by Revel *et al.*;[11] ††the result could be unreliable in the setting of acute clot and/or anticoagulation: abnormal parameters were systematically reassessed away from the acute phase and after anticoagulant cessation; *diagnosis performed using diluted Russell viper venom time (dRVVT LAC-Screen/confirm® Siemens), PTT-LA-Stago and Staclot-LA® Stago if needed; **quantified using chemiluminescence assays (Acustar®, Werfen); ***no patient had confirmed natural inhibitor deficiency after anticoagulant cessation.



ABBREVIATION LIST:

COVID-19 = Coronavirus disease;

CTPA = computed tomography pulmonary angiography;

DVT = deep vein thrombosis;

ICU = intensive care unit;

LMWH = low-molecular-weight heparin;

PE = pulmonary embolism;

SARS-CoV-2 = severe acute respiratory syndrome coronavirus;

UFH = Unfractionated heparin

VTE = venous thromboembolic event